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Noonan Syndrome: A Cryptic Condition in Early Gestation

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Noonan syndrome is one of the most common of genetic syndromes and manifests at birth, yet it is usually diagnosed during childhood. Although prenatal diagnosis of Noonan syndrome is usually not possible, in a few cases the ultrasonographic findings suggested the diagnosis in utero. Reported sonographic clues include septated cystic hygroma, hydrothorax, polyhydramnios, and cardiac defects, such as pulmonic stenosis and hypertrophic cardiomyopathy. During a 6-year period, 46,224 live-born infants were delivered at the Chaim Sheba Medical Center. Seven newborn infants and four fetuses were found to have Noonan syndrome. One fetus showed transient nuchal translucency of 4 mm and bilateral neck cysts at the 13th gestational week. Both findings resolved spontaneously by the 18th gestational week, but during the third trimester this fetus developed hydrothorax, skin edema, and polyhydramnios. In the three other fetuses, first- and second-trimester ultrasonographic findings were normal, and the diagnosis of Noonan syndrome was suggested only during the third trimester. All three fetuses had polyhydramnios and skin edema. A cardiac malformation, hydrothorax, and a large head were present in one fetus. Sonographic facial findings were investigated. In all four fetuses posteriorly angulated, apparently low-set ears and depressed nasal bridge were identified. Wide nasal base was seen in two fetuses. In two fetuses, persistent opening of the fetal mouth was interpreted as fetal hypotonia. One fetus developed progressive postnatal hypertrophic cardiomypathy and in one case, pulmonic stenosis became apparent at age 6 months. This small series suggests that Noonan syndrome has an evolving phenotype during in utero and postnatal life. Amelioration of early nuchal region findings and late onset of the more "typical" ultrasonographic changes may limit early prenatal detectability. Am. J. Med. Genet. 92:159–165, 2000.

KEY WORDS: Noonan syndrome; ultrasonographic studies; prenatal diagnosis; nuchal

INTRODUCTION

Noonan syndrome is a multiple congenital anomaly syndrome comprising typical facial changes and various somatic abnormalities, including short stature, lymphedema, genital anomalies, and cardiac defects. In one series, mental retardation was reported in 11% of cases, and the mean age at diagnosis was 9 years, despite the distinctive phenotype [Sharland et al., 1992]. The delay in diagnosis probably reflects the evolving phenotype [Allanson et al., 1985]. The reported incidence of the syndrome is 1:1,000 to 1,500 live births, and it may be sporadic or autosomal dominant. The pathogenesis is unknown, and the expression is variable [Mendez and Opitz, 1985; Allanson, 1987]. A gene for Noonan syndrome was mapped to chromosome 12 [Jamieson et al., 1994].

Although Noonan syndrome (NS) is one of the most common genetic diseases, there are no definitive ultrasonographic criteria for early in utero recognition. Lymphedema, cystic hygroma, and cardiomyopathy during late stages of gestation were reported in fetuses with Noonan syndrome [Zarabi et al., 1983; Witt et al., 1987; Benacerraf et al., 1989; Izquierdo et al., 1990; Donnefeld et al., 1991; Sonesson et al., 1992]. Recently,

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with the introduction of early ultrasonographic screening for fetal aneuploidy, fetuses with "nuchal translucency" and normal karyotype were occasionally found to have Noonan syndrome [Johnson et al., 1993; Trauffer et al., 1994; Souka et al., 1998]. In the present report we describe four fetuses suspected to have Noonan syndrome while still in utero. In addition, we review similar reports and discuss the feasibility of early prenatal diagnosis of the syndrome and its limitations.

MATERIAL AND METHODS

In Israel, most pregnant women are having three ultrasonographic studies, one in each trimester. In the greater Tel Aviv area, second-level sonograms are also commonly performed, and women with abnormal sonograms are usually referred to a specialized center. The Chaim Sheba Medical Center (CSMC) is such a tertiary referral center. Beginning on 1/1/1993 through 31/12/1998, 12,124 prenatal ultrasonograms were performed for various reasons, and cases suspected prenatally as having NS were closely followed throughout pregnancy.

During these 6 years, 46,224 newborn infants were delivered at the CSMC and a single medical geneticist (MF) examined all of those with malformations or abnormal facial appearance (as judged by the neonatologists). Because length is not routinely measured (Ministry of Health regulation), cases presenting with mild or moderate short stature as their only manifestation were largely not examined. A karyotype was performed in all newborn infants suspected of NS and they were subsequently seen at least once in a follow-up visit to the genetics clinic. In addition, medical records of all cases born at CSMC during the study period who were diagnosed during the first year of life as having NS, were reviewed retrospectively. Because of the HMO's referral policy, this period was not extended to include older patients.

RESULTS

Four fetuses in whom prenatal ultrasonographic findings suggested NS were examined postnatally and the diagnosis was confirmed. In addition to the four patients diagnosed prenatally, two newborns and five infants were diagnosed as having NS. Routine ultrasound findings were normal in all these seven cases.

In three of the four NS fetuses, first- and second-trimester scans were normal. One fetus (case 2), had increased nuchal translucency of 4 mm and bilateral neck cysts at 13 weeks of gestation. However, all nuchal findings resolved spontaneously by 18 weeks of gestation. Subsequently, bilateral hydrothorax, probably reflecting abnormal lymphatic drainage, developed during the third trimester. Similarly, hydrothorax was the presenting symptom in fetus 3, in whom two previous scans during the first and second trimester were normal.

Polyhydramnios and skin edema appeared in all four cases during the third trimester. Congenital cardiac disease was documented prenatally only in fetus 1. In this fetus, an atrio-ventrical (A-V) canal was detected at the third trimester, but detailed echocardiographic examination was not performed in the early stages of gestation. In fetuses 2, 3, and 4, NS was suspected, and detailed echocardiographic examination was performed. Only in case 3 could thickening of the pulmonic valve be demonstrated in the third trimester. In the 2 remaining cases, despite detailed and repeated echocardiographic studies, pulmonic stenosis (case 2) and hypertrophic cardiomyopathy (case 4) developed progressively only after birth. A small muscular ventricular septal defect (VSD) was missed in fetus 4. Distinctive facial manifestations could be recognized in all four fetuses during the third trimester. These included depressed and wide nasal bridge, short chin, thick, rotated ears, and prominent upper lip. Persistently open mouth detected in fetuses 1 and 4 was interpreted as reflecting fetal hypotonia. The sonographic and clinical findings are illustrated in Figures 1 (case 1), 2, and 3 (case 2). The clinical findings are summarized in Table I.

The seven cases diagnosed postnatally fulfilled accepted criteria for the diagnosis of NS (data not shown) [Sharland et al., 1992].

DISCUSSION

Noonan syndrome is a relatively common genetic disease affecting between 1:1,000 and 1:1,500 newborns [Mendez and Opitz, 1985]. Thus, it can be assumed that during the study period, some 30 to 46 NS patients would have been born at CSMS. However, only 11 cases were diagnosed before or after birth. Since an experienced medical geneticist is summoned for consultation in all cases of malformed infants and newborn infants with an abnormal appearance, it is reasonable to assume that most cases of NS do not present the typical phenotype at birth. This view is supported by the observations of Allanson et al. [1985] and Sharland et al. [1992]. In view of the difficulty to establish a postnatal diagnosis, it is not surprising that despite the distinctive phenotype and the common association with congenital lymphatic and cardiac abnormalities, only six reports of prenatal sonographic features of Noonan syndrome were found in the literature [Zarabi et al., 1983; Witt et al., 1987; Benacerraf et al., 1989; Izquierdo et al., 1990; Donnefeld et al., 1991; Sonesson et al., 1992]. In only two reports was the diagnosis of Noonan syndrome suspected during pregnancy [Benacerraf et al., 1989; Donnefeld et al., 1991], whereas other authors described sonographic findings retrospectively in patients diagnosed postnatally. In the 12 reported cases that had prenatal sonographic evaluation, skin edema was present in two, generalized hydrops in five, and nuchal cystic hygroma of the septated type and hydramnios in all 12. Although five fetuses had cardiac malformations, only two were detected prenatally. Early sonographic data, obtained between 12 and 14 weeks of gestation, were available in three cases; two had cystic hygroma and one was normal. In one of the two, cystic hygroma subsequently resolved and left a skin web recognized by ultrasound and confirmed after delivery [Donnefeld et al., 1991].

Fig. 1. Patient 1. **A:** Mid-sagittal ultrasound view shows depressed nasal root and semi-open mouth. **B:** In this sagittal view obtained laterally to the previous, a thickened folded helix inclined posteriorly is depicted. **C:** Sagittal view of the neonate. Note the similarity with prenatal ultrasound images: thickened folded ear, semi-open mouth, and depressed nasal bridge. The short neck and skin edema are characteristic of Noonan syndrome.

Because all fetuses in this cumulative series have shown midtrimester, cervical cystic hygroma, this finding was considered by Benaceraff et al. [1989] as the earliest reliable sign for in utero diagnosis of Noonan syndrome. However, none of our cases had evidence of septated cystic hygroma, and only one of the fetuses examined at early stages of gestation had transient nuchal translucency of 4 mm with bilateral neck cysts. This observation indicates that cervical lymphatic abnormalities are not a sine qua non for a prenatal diagnosis of Noonan syndrome.

Witt et al. [1987] suggested that lymphedema in Noonan syndrome may involve either localized areas or the entire body. Furthermore, in individual patients

Fig. 2. Patient 2. Mid-sagittal ultrasonographic view of the fetus at 13 weeks of gestation showing increased nuchal translucency (arrowheads).

lymphedema may present at different ages, beginning in the prenatal period and extending through adulthood. Although Noonan syndrome may manifest at birth, many patients never have lymphedema [Allanson et al., 1985], probably because it had resolved in utero, as illustrated by our second case. Thus, the timing of appearance and regression of the nuchal findings may influence the sonographic detectability of Noonan syndrome.

Nuchal translucency is the ultrasonographic term describing the changes in the fetal neck region during the first trimester. This finding should be differentiated from the septated cystic hygroma seen later during the second trimester [Bronshtein et al., 1993]. Second-trimester, septated nuchal hygroma is usually associated with an underlying pathology, such as chromosomal aneuploidy and congenital heart defects [Jones, 1988; Chitayat et al., 1989]. Although, first-trimester fetal nuchal translucency may be a normal developmental phenomenon [Nishimura and Okamoto, 1976; Wilson et al., 1992; Achiron et al., 1995; Moscoso, 1995], excessive nuchal translucency in the 10- to 14-gestational week window is a risk factor for chromosomal aneuploidy [Souka et al., 1998].

The association of nuchal translucency with Noonan syndrome has been anecdotal. Johnson et al. [1993] found one case of Noonan syndrome among 27 fetuses with transient nuchal translucency of >3 mm and normal karyotype. Likewise, Trauffer et al. [1994] reported that 1 of 22 such fetuses had Noonan syndrome. In a prospective follow-up study, Boyd et al. [1996] showed that among 19 fetuses with nuchal translucency who continued the pregnancy, Noonan syndrome was suspected in two, one of whom died in utero.

Recently Souka et al. [1998] reviewed 4,116 chromosomally normal pregnancies with increased fetal nuchal translucency. They found one case with Noonan syndrome, and five more cases in their literature survey. However, all fetuses had nuchal thickness greater than 6 mm. This extent of nuchal translucency is definitively considered an hygroma. The results of Souka et al. [1998] represent a database of 100,113 pregnancies specifically monitored for nuchal translucency [Nikolaides, personal communication]. With the reported prevalence of the syndrome, at least 70 cases of NS would have been expected in this patient population. In view of these results, it appears that moderate nuchal translucency has only a minor contribution to the diagnosis of fetal Noonan syndrome.

Although almost all heart defects were reported in NS, the "pathognomonic" cardiac abnormalities are pulmonic stenosis, atrial septal defect, and hypertrophic cardiomyopathy. Unfortunately, pulmonic stenosis and atrial septal defect are rarely detectable in utero, as illustrated by our second case, in whom pulmonic stenosis was missed on detailed cardiac echocardiographies at 20 and 28 weeks. Asymmetric septal hypertrophy is a progressive anomaly that becomes more evident postnatally, as illustrated by our case 4. The observation that hypertrophic cardiomyopathy is an evolving phenomenon is supported by other reports [Noonan and O'Connor, 1996; Sharland et al., 1992]. Previously, Sonenson et al. [1992] reported on a fetus evaluated by echocardiography at 23 weeks of gestation because of cystic hygroma. Only in a subsequent examination at 35 weeks of gestation, prominent septal hypertrophy was identified.

With the introduction of high-resolution ultrasound equipment, it is now possible to visualize minor facial anomalies and some fetal facial expressions [Birnholz, 1995]. The faces of the four fetuses were scanned in appropriate planes to obtain optimal visualization of the nasal bridge, inter-alar distance, mouth, upper and lower lips, ear position, and morphology. The sonographic facial findings in these fetuses were unusual. Although in utero diagnosis based on minor facial anomalies has never been reported, the similarity between the scans obtained in utero and the ex utero appearance is impressive. Collection of similar images at different stages of pregnancy may facilitate prenatal recognition of syndromes with distinctive facial phenotype.

The clinical course of the four fetuses presented in this report was severe and resulted in early death or significant handicap. Despite this severe course, the early sonograms were either normal or showed tran-

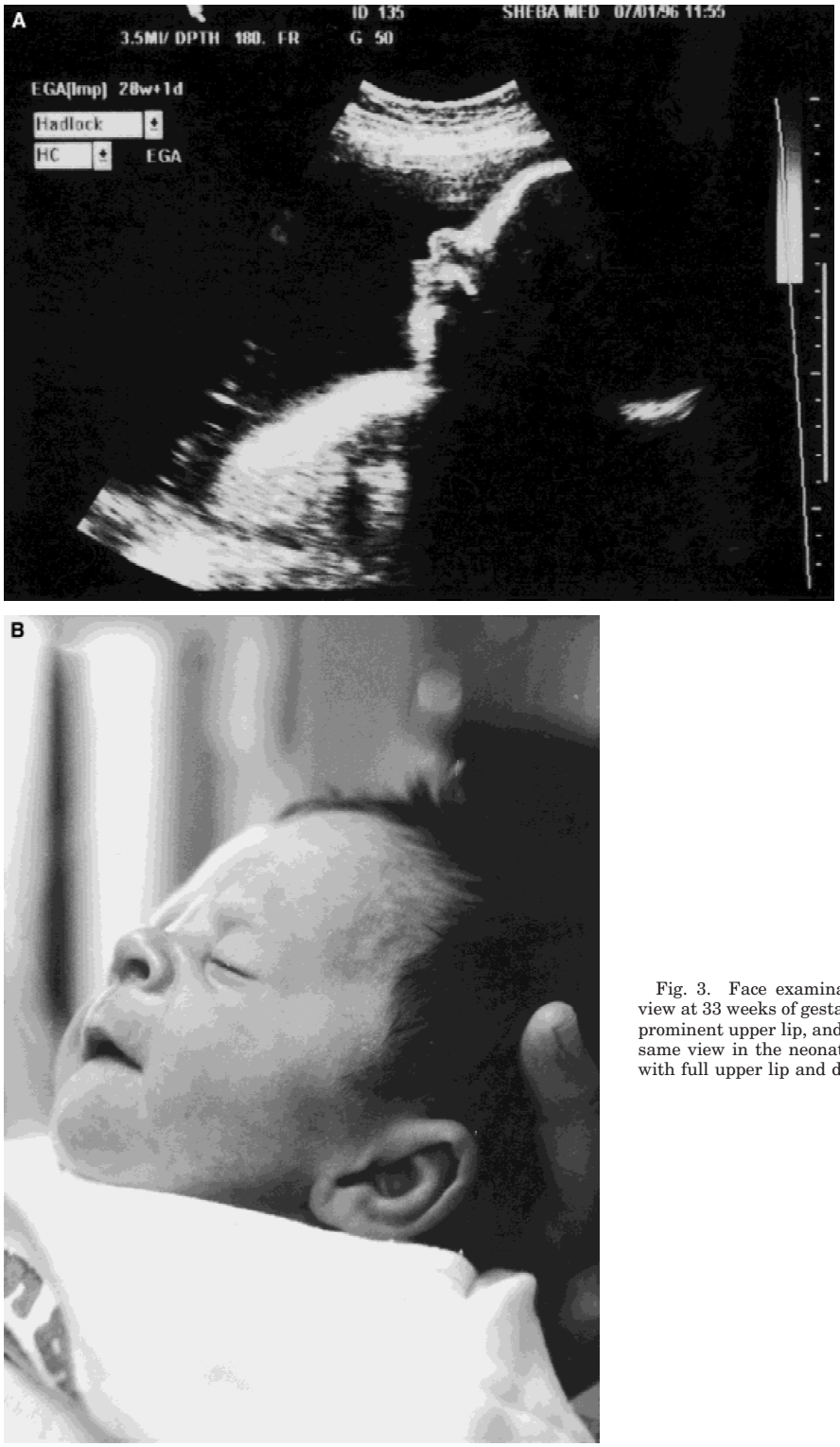

Fig. 3. Face examination of Patient 2. **A:** Sagittal ultrasonographic view at 33 weeks of gestation reveals upturned nose, depressed nasal root, prominent upper lip, and mild retrognanthia can be demonstrated. **B:** The same view in the neonate shows apparently low-set ears and small chin with full upper lip and depressed nasal bridge.

sient findings, and the correct diagnosis was suspected only in the third trimester. It is conceivable that the "average" cases have only soft sonographic manifestations, which can be overlooked or misinterpreted. Souka's [1998] recent results indicate that most patients with significant nuchal translucency do not have Noonan syndrome. Taken together, these observations suggest that Noonan syndrome is a cryptic condition in early gestation. On the other hand, overt second-trimester manifestations may predict a severe postnatal course and should be adequately addressed in genetic counseling.

TABLE I. Clinical Findings*

Patient	1	2	3	4
Maternal age	23	32	28	43
Family history	No	Short mother	No	No
Gestational age at scan	31	13, 18, 20, 28, 32	12, 24, 28, 32	14, 20, 35
Triple test	Normal	Normal	Normal	Normal
Karyotype	46,XX	46,XX	46,XY	46,XY
Indication for referral	LGA	Routine	Hydrothorax	Large head, polyhydramnion
First trimester	ND	Nuchal translucency and cysts	Normal	Normal
Second trimester	ND	Normal	Normal	Normal
Third trimester				
Size	LGA	AGA	AGA	LGA
Polyhydramnion	+	+	+	+
Nuchal region	Normal	Normal	Normal	Normal
Cardiac anomaly	A-V canal	Pulmonic stenosis	Thick pulmonic valve	VSD Cardiomyopathy
Renal	Pyelectasis	Normal	Normal	Normal
Skin edema	+	+	+	+
Effusion	Post natal	+	Hydrothorax	–
Prenatal facial findings				
Nasal root	Depressed	Depressed	Depressed	Depressed
Nose	Wide base	Small, upturned	Wide base	
Short chin	+	+	Triangular	
Open mouth	+			+
Tongue protrusion	–	–	–	–
Ear anomaly	Posteriorly rotated, thick folded helix	Low-set	Low-set, thick, folded helix	Thick, folded helix
Upper lip	Prominent	Protruding	Normal	Protruding
Postnatal clinical findings				
Birth weight/age (weeks)	3,100 (37)	2,615 (34)	2,000 (34)	4,050 (39)
Ocular hypertelorism	–	+		
Palpebral fissures	Downslant	Downslant	Horizontal	Downslant
Epicanthal folds	+	+	–	+
Ptosis	+	+	–	–
Simian line	–	+	–	–
Hypotonia	–	+	–	+
Other findings				Cryptorchidism Short webbed neck
Follow-up and outcome	Neonatal death due to cardiac failure	2 years of follow-up; developmental delay, hypotonia	Neonatal death, due to respiratory failure; hydrothorax; thick pulmonic valve at autopsy	4½ month; progressive cardiomyopathy; hepatomegaly, widely spaced nipples; pes varus; developmental delay; short stature; external hydrocephalus

*ND, not done; LGA, large for gestational age; AGA, appropriate for gestational age; A-V, atrio-ventrical; VSD, ventricular septal defect; +, present; –, absent.

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